

A clean technology of producing 16-dehydropregnenolone and its analogs

Technical Field

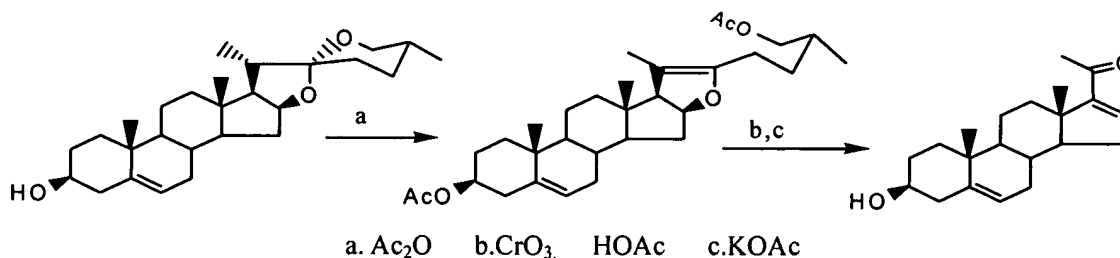
The invention relates to a clean process for the degradation of steroidal sapogenin to produce 16-dehydropregnenolone and its analogs.

Background Art

16-Dehydropregnenolone (3 β -hydroxypregn-5(6),16(17)-diene-20-one) is the hydrolysate of 16-Dehydropregnenolone acetate which is called 'diene' in industry. Its analogs include 3 β -hydroxy-5 α -pregn-16(17)-ene-20-one, 3 β -hydroxy-5 β -pregn-16(17)-ene-20-one, 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one, 3 β ,12 α -dihydroxy-5 α -pregn-16(17)-ene-20-one, 3 β -hydroxy-5 α -pregn-12,20-dione.

16-Dehydropregnenolone acetate and 3 β -hydroxy-5 α -pregn-16(17)-ene-20-one acetate are important intermediates of steroidal hormone drugs. The throughput of the two compounds is kiloton and several hundred ton in China each year, respectively.

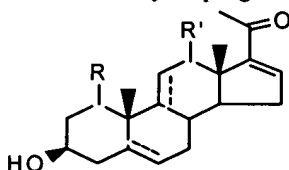
But the technique of manufacturing the two compounds used today is still based on the old degradation method of steroidal sapogenin which was developed by Marker, an American chemist, in the 40' last century (Marker: *J.Am.Chem.Soc.*1940,62, 3350. 1941,63, 774. 1947, 69 2167). It can be described below: in acetic anhydride and acetic acid, under high pressure and at high temperature (above 200°C), steroidal sapogenin is degraded to pseudo steroidal sapogenin, which is oxidized by chromate. After elimination, the corresponding 16-Dehydropregnenolone is obtained. The overall yield is about 60% for the three steps. Taking diosgenin for example, it can be outlined below:



Though this method had been ameliorated successively, the shortcomings still exist. One of the shortcomings is the oxidation with chromate in the procedure, which caused serious environmental pollution. Therefore, Professor Weisheng Tian and his co-workers had opened out the research of how to utilize steroidal sapogenin rationally since 1991.

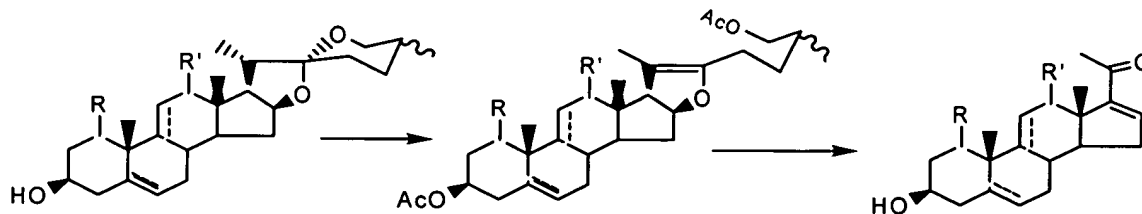
The present invention is the extending of Tian's prevenient inventions (Weisheng Tian, et al, Chinese patent, patent No: 96116304.6; Chinese patent, application No: 00127974.2; Chinese patent, application No: 01113196.9 etc).

In this invention, the pseudo steroidal sapogenin, degraded from steroidal sapogenin without purification, is oxidized with hydrogen peroxide (instead of chromate) in organic solvent with or without metal catalysts. After elimination and hydrolization, the corresponding 16-Dehydropregnenolone or its analog is obtained. Another product, 4R(or S)-methyl-pentyl lactone, is produced in the process. The mentioned steroidal sapogenin includes: diosgenin, tigogenin, sarsasapogenin, hecogenin, and other natural steroidal sapogenin. It also includes the analogs modified from natural steroidal. The structure of 16-dehydropregnenolone and its analogs can be outlined below:



The invention relates to a clean process for the degradation of steroidal sapogenin to produce 16-dehydropregnenolone and its analogs.

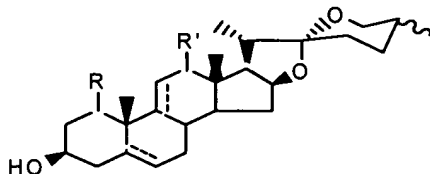
In this invention, the pseudo steroidal sapogenin, degraded from steroidal sapogenin, is oxidized with hydrogen peroxide (instead of chromate) in organic solvent with or without metal catalysts. After elimination and hydrolization, the corresponding 16-Dehydropregnenolone or its analog is obtained. Another product, 4R(or S)-methyl-pentyl lactone, is produced in the process. For example:



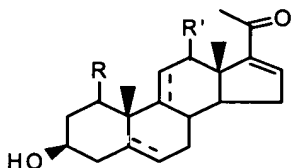
Firstly, steroidal sapogenin is degraded to pseudo steroidal sapogenin under high pressure according to known method. Then, the pseudo steroidal sapogenin went through oxidation, elimination and hydrolization. 16-Dehydropregnenolone or its analog is obtained, accompanied with 4R(or S)-methyl- δ -pentyl lactone.

The crude degradation product is dissolved in organic solvent, and then hydrogen peroxide, metal catalyst and acid are added. The molar ratio of pseudo steroidal sapogenin, hydrogen peroxide, metal catalyst and acid is 1:1.0-4.0:0.001-1:0-1, of which 1:1.5-2.5:0.005-0.02:0 is preferred. The reaction temperature is 0-80°C. The reaction time is 10 min to 24 hour. The reaction is monitored by chromatogram until the starting material disappeared. The mixture is refluxed with base for 0.5-2 hour to completely convert the unreacted 16-carboxoyl-20-one to 16-Dehydropregnenolone or its analog, accompanied with the other product 4R(or S)-methyl-5-hydroxy-pentate. Remove part of the organic solvent under reduced pressure then add water to precipitate 16-Dehydropregnenolone or its analog. The water layer is acidified and extracted with organic solvent to give 4R(or S)-methyl- δ -pentyl lactone.

The mentioned steroidal sapogenin is of the structure:



The structure of the mentioned 16-dehydropregnenolone and its analogs can be outlined below:



The mentioned metal catalyst include: tungstic oxide (WO_3), tungstate, vanadic acid, vanadate, vanadyl acetylacetonate, molybdic anhydride (MoO_3), molybdate, phosphomolybdate, heteropolyacid, heteropolyate.

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phthalic acid and isophthalic acid, the sulfonic acid is preferable to be benzenesulfonic acid and p-toluene sulphonic acid, and the inorganic acid is preferable to be sulfuric acid (H_2SO_4), phosphoric acid (H_3PO_4) and phosphorous acid (H_3PO_3).

The mentioned organic solvent include dihalogen methane, trihalogen methane, dichloroethane, ethanol (EtOH), butanol (BuOH), t-butanol (t-BuOH), dimethyl sulphoxide (DMSO), N,N-dimethylformamide (DMF), acetone, butanone, cyclohexanone, acetonitrile, ethyl acetate and acetic acid.

The mentioned base include: hydroxid, carbonate and bicarbonate, preferably to be sodium hydroxide (NaOH), potassium hydroxide (KOH), lithium hydroxide (LiOH), cesium hydroxide (CsOH), sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), lithium carbonate (Li_2CO_3), cesium carbonate (Cs_2CO_3), sodium bicarbonate (NaHCO_3) and potassium bicarbonate (KHCO_3).

This invention had been verified in hundred-gram scale for several times. This technology improved the utilizing degree of steroidal sapogenin, improved the yield, and cleared up the chromium pollution in former technique. In a word, the method disclosed in this invention is more suitable for manufacture.

EXAMPLES

The invention is illustrated below with reference to the following examples. Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

Example 1

Degradation of sarsasapogenin to 3β -hydroxy- 5β -pregn-16(17)-ene-20-one and 4S-methyl- δ -pentyl lactone:

10g of sarsasapogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then 3.3mg of $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (0.01mmol) and 5ml of hydrogen peroxide (30% H_2O) were added, and this mixture was stirred for 2 hours at 80°C . The low boilers were removed under reduced pressure and the residue was dissolved in 50ml of EtOH, and refluxed for 2 hours with 5% LiOH. The mixture was concentrated, diluted with water, and filtrated to get 6.3g of 3β -hydroxy- 5β -pregn-16(17)-ene-20-one in 84% yield. m.p. $186-8^\circ\text{C}$, $^1\text{H-NMR}$ (300MHz, CDCl_3) δ (ppm): 6.61(dd, $J=1.3\text{Hz}$, 1H, 16-H), 3.5 (m, 1H, 3-H), 2.26(s, 3H, CH_3CO -, 21-H), 0.84(s, 3H, 18-H), 0.88(s, 3H, 19-H). MS(m/z, %): 316(M^+), 301($\text{M}^+ - \text{CH}_3$), 283($\text{M}^+ - \text{CH}_3 - \text{H}_2\text{O}$), 159, 145, 115, 105, 91, 43. The water layer was acidified and extracted with organic solvent to give 2.1g of 4S-methyl- δ -pentyl lactone in 80% yield. $[\alpha]_D^{20} = -13^\circ$ (c 0.8, CHCl_3), IR(v): 2950, 1730, 1340, 1210, 1190, 1040 cm^{-1} . $^1\text{H-NMR}$ (300MHz, CDCl_3) δ (ppm): 0.96(d, 3H, $J=6.6\text{Hz}$), 1.88-2.06(m, 2H), 1.43-1.56(m, 1H), 3.83-3.90(m, 1H), 4.23-4.29(m, 1H). MS(m/z, %): 115($\text{M}^+ + 1$), 114(M^+), 109, 56, 42.

Example 2

Degradation of sarsasapogenin to 3 β -hydroxy-5 β -pregn-16(17)-ene-20-one and 4S-methyl- δ -pentyl lactone:

100g of sarsasapogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 500ml of BuOH. 23mg of WO₃ (0.01mmol), 10g of isophthalic acid and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After 5% KOH was added, it was kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 66g of 3 β -hydroxy-5 β -pregn-16(17)-ene-20-one in 88% yield. The water layer was acidified and extracted with organic solvent to give 22g of 4S-methyl- δ -pentyl lactone in 84% yield.

Example 3

Degradation of sarsasapogenin to 3 β -hydroxy-5 β -pregn-16(17)-ene-20-one and 4S-methyl- δ -pentyl lactone:

100g of sarsasapogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 500ml of BuOH. 23mg of WO₃ (0.01mmol), 1g of isophthalic acid and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After 5% KOH was added, it was kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 60g of 3 β -hydroxy-5 β -pregn-16(17)-ene-20-one in 80% yield. The water layer was acidified and extracted with organic solvent to give 22g of 4S-methyl- δ -pentyl lactone in 84% yield.

Example 4

Degradation of diosgenin to 16-dehydropregnenolone and 4R-methyl- δ -pentyl lactone:

100g of diosgenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then 3.3mg of (NH₄)₂MoO₄ (0.01mmol), 5g of benzoic acid and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. The low boilers were removed under reduced pressure and the residue was dissolved in 500ml of cyclohexatone, and refluxed for 2 hours with 5% CsOH. The mixture was concentrated, diluted with water, and filtrated to get 64g of 16-dehydropregnenolone in 84% yield. m.p. 168-170°C, ¹H-NMR (300MHz, CDCl₃) δ (ppm): 6.72(dd, J=1.3Hz, 1H, 16-H), 5.38(d, J=4Hz, 1H, 6-H), 2.26(s, 3H, CH₃CO-, 21-H), 0.85(s, 3H, 18-H), 0.88(s, 3H, 19-H). MS(m/z, %): 314(M⁺), 299(M⁺-CH₃), 281(M⁺-CH₃-H₂O), 253, 239, 229, 203, 159, 145, 115, 105, 91, 43. The water layer was acidified and extracted with organic solvent to give 22g of 4R-methyl- δ -pentyl lactone in 80% yield. b.p. 83-89°C/15mmHg, [α]_D²⁰ = +13.6° (c 0.9 CHCl₃), IR(v): 2950, 1730, 1340, 1210, 1190, 1040cm⁻¹. ¹H-NMR (300MHz, CDCl₃) δ (ppm): 0.96(d, 3H, J=6.6Hz), 1.88-2.06(m, 2H), 1.43-1.56(m, 1H), 3.83-3.90 (m, 1H), 4.23-

4.29 (m, 1H). MS(m/z, %): 115(M⁺+1), 114(M⁺), 109, 56, 42.

Example 5

Degradation of diosgenin to 16-dehydropregnenolone and 4R-methyl- δ -pentyl lactone:

100g of diosgenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 500ml of EtOH. 182mg of ammonium phosphomolybdate ((NH₄)₃[P(Mo₁₂O₄₀)]·6H₂O, 0.1mmol) and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After NaHCO₃ was added, it was kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 72g of 16-dehydropregnenolone in 95% yield. The water layer was acidified and extracted with organic solvent to give 24g of 4R-methyl- δ -pentyl lactone in 88% yield.

Example 6

Degradation of diosgenin to 16-dehydropregnenolone and 4R-methyl- δ -pentyl lactone:

100g of diosgenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 500ml of EtOH. 3.48g of VO(acac)₂ and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After NaHCO₃ was added, it was kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 71g of 16-dehydropregnenolone in 93% yield. The water layer was acidified and extracted with organic solvent to give 24g of 4R-methyl- δ -pentyl lactone in 88% yield.

Example 7

Degradation of diosgenin to 16-dehydropregnenolone and 4R-methyl- δ -pentyl lactone:

10g of diosgenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 50ml of dichloromethane. 18mg of (NH₄)₃[P(Mo₁₂O₄₀)]·6H₂O (0.1mmol) and 5ml of hydrogen peroxide (30%H₂O) were added, and this mixture was refluxed for 2 hours. After K₂CO₃ was added, it was kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 7.2g of 16-dehydropregnenolone in 95% yield. The water layer was acidified and extracted with organic solvent to give 2.4g of 4R-methyl- δ -pentyl lactone in 88% yield.

Example 8

Degradation of diosgenin to 16-dehydropregnenolone and 4R-methyl- δ -pentyl lactone:

100g of diosgenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 500ml of t-BuOH. 23mg of WO₃, 2ml of H₃PO₄ and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After KOH was added, it was

kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 70g of 16-dehydropregnenolone in 92% yield. The water layer was acidified and extracted with organic solvent to give 23g of 4R-methyl- δ -pentyl lactone in 84% yield.

Example 9

Degradation of tigogenin to 3 β -hydroxy-5 α -pregn-16(17)-ene-20-one and 4R-methyl- δ -pentyl lactone:

100g of tigogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 500ml of BuOH. 200mg of Na₃[P(W₁₂O₄₀)] and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After NaOH was added, it was kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 70g of 3 β -hydroxy-5 α -pregn-16(17)-ene-20-one in 92% yield. m.p. 207-9°C, $[\alpha]_D^{20} = +51^\circ$ (c 0.9 CHCl₃), ¹H-NMR (300MHz, CDCl₃) δ (ppm): 6.59(dd, J=1.3Hz, 1H, 16-H), 3.45(m, 1H, 3-H), 2.26(s, 3H, CH₃CO-, 21-H), 0.83(s, 3H, 18-H), 0.89(s, 3H, 19-H). MS(m/z, %): 316(M⁺), 301(M⁺-CH₃), 283(M⁺-CH₃-H₂O), 159, 145, 115, 105, 91, 43. The water layer was acidified and extracted with organic solvent to give 21g of 4R-methyl- δ -pentyl lactone in 80% yield.

Example 10

Degradation of tigogenin to 3 β -hydroxy-5 α -pregn-16(17)-ene-20-one and 4R-methyl- δ -pentyl lactone:

10g of tigogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 50ml of DMF. 48mg of Na₂MoO₄·2H₂O (0.2mmol), 0.1ml of H₂SO₄ and 5ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After KOH was added, it was kept on stirring for 2 hours at 80°C. The mixture was diluted with water and filtrated to get 6.8g of 3 β -hydroxy-5 α -pregn-16(17)-ene-20-one in 90% yield. The water layer was acidified and extracted with organic solvent to give 2.3g of 4R-methyl- δ -pentyl lactone in 84% yield.

Example 11

Degradation of tigogenin to 3 β -hydroxy-5 α -pregn-16(17)-ene-20-one and 4R-methyl- δ -pentyl lactone:

100g of tigogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then 186mg of H₇[(PMo₂O₇)₆]·xH₂O (0.1mmol) and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. The low boilers were removed under reduced pressure and the residue was dissolved in 500ml of EtOH containing 5% KOH, and refluxed for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 65g of 3 β -hydroxy-5 α -pregn-16(17)-ene-20-one in 86% yield. The water layer was acidified and extracted

with organic solvent to give 22g of 4R-methyl- δ -pentyl lactone in 80% yield.

Example 12

Degradation of rockogenin to 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one and 4R-methyl- δ -pentyl lactone:

100g of rockogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 500ml of BuOH. 30mg of V₂O₅(0.2mmol), 1ml of phosphorous acid and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After KOH was added, it was kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 70g of 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one in 91% yield. m.p.203-205°C, $[\alpha]_D^{25} = +2.0$ (c=1.00 CHCl₃), IR(v): 1645, 1580 cm⁻¹, ¹H-NMR (300MHz, CDCl₃) δ (ppm): 6.90 (m,1H,16-H),2.37 (s,3H, CH₃CO-, 21-H),0.87 (s,3H, 18-H), 0.82(s,3 H, 19-H). The water layer was acidified and extracted with organic solvent to give 23g of 4R-methyl- δ -pentyl lactone in 84% yield.

Example 13

Degradation of rockogenin to 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one and 4R-methyl- δ -pentyl lactone:

100g of rockogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 500ml of BuOH. 30mg of MoO₃, 1ml of phosphorous acid and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 3 hours at 80°C. After KOH was added, it was kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 70g of 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one in 91% yield. The water layer was acidified and extracted with organic solvent to give 23g of 4R-methyl- δ -pentyl lactone in 84% yield.

Example 14

Degradation of rockogenin to 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one and 4R-methyl- δ -pentyl lactone:

100g of rockogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 500ml of BuOH. 30mg of WO₃(0.2mmol), 1ml of phosphorous acid and 50ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After KOH was added, it was kept on refluxing for 2 hours. The mixture was concentrated, diluted with water, and filtrated to get 71g of 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one in 92% yield. The water layer was acidified and extracted with organic solvent to give 23g of 4R-methyl- δ -pentyl

lactone in 84% yield.

Example 15

Degradation of rockogenin to 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one and 4R-methyl- δ -pentyl lactone:

10g of rockogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 50ml of DMSO. 24mg of Na₂MoO₄·2H₂O (0.1mmol), 1ml of H₃PO₄ and 5ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After Li₂CO₃ was added, it was kept on stirring for 2 hours at 80°C. The mixture was diluted with water and filtrated to get 7.2g of 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one in 94% yield. The water layer was acidified and extracted with organic solvent to give 2.4g of 4R-methyl- δ -pentyl lactone in 88% yield.

Example 16

Degradation of rockogenin to 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one and 4R-methyl- δ -pentyl lactone:

10g of rockogenin, dissolved in acetic acid and acetic anhydride, was kept in the pressure kettle at 200°C for one hour, then the low boilers were removed under reduced pressure and the residue was dissolved in 50ml of DMSO. 24mg of Na₂MoO₄·2H₂O (0.1mmol), 1g of butyric acid and 5ml of hydrogen peroxide (30%H₂O) were added, and this mixture was stirred for 2 hours at 80°C. After Li₂CO₃ was added, it was kept on stirring for 2 hours at 80°C. The mixture was diluted with water and filtrated to get 7.2g of 3 β ,12 β -dihydroxy-5 α -pregn-16(17)-ene-20-one in 94% yield. The water layer was acidified and extracted with organic solvent to give 2.4g of 4R-methyl- δ -pentyl lactone in 88% yield.